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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/647,789	08/25/2003	Daniel P. Wermeling	INT-001 B	2016
51414 7590 10/19/2007 GOODWIN PROCTER LLP PATENT ADMINISTRATOR EXCHANGE PLACE BOSTON, MA 02109-2881			EXAMINER BETTON, TIMOTHY E	
			ART UNIT 1614	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/647,789

Applicant(s)

WERMELING, DANIEL P.

Examiner

Timothy E. Betton

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 July 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 7, 8, 10-13, 16-20, 46-67 and 70-72 is/are pending in the application.
- 4a) Of the above claim(s) 1-4, 7, 8, 10-13, 16-20 and 46-52 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 53-67 and 70-72 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

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DETAILED ACTION

Applicants' Remarks filed 9 July 2007 have been acknowledged and made of record.

Applicants assert the amendments to claims 53, 54, 62-67, and 70, and the explanation for the lack of units in claims 65 and 70 address the rejections noted in the Office Action.

Applicants assert further that the Office appears to be relying upon the teachings of Ward-Smith to make up for the deficiencies in Weinstein and Levin. Applicant agrees that Ward-Smith describes certain measurements for characterizing spray plumes, for example, Dv10, Dv50 and Dv90 measurements. However, Ward-Smith is completely silent about the particular plume geometry that should be created to provide the results described in Example 1 of the application. Applicant submits that none of the applied references, either alone or in combination, teach an opioid containing device, which upon positioning 5 cm away from a laser beam detection pathway, actuating the device to produce a spray plume perpendicular to said pathway, and detecting droplet size distribution of the spray plume with said laser beam detection pathway, produces a spray plume having a Dv1 0 of from about 14.3 micro.m to about 17.1 micro.m and a Dv50 of from about 31.0 micro.m to about 35.3 micro.m.(page 10-11, bottom paragraph).

However, these arguments are not found persuasive and the 103(a) is maintained. The references (already of record) of Weinstein, Levin, and Ward-Smith in combination or incorporated together teach the subject matter of claimed invention. The central issue of the invention is drawn to an intranasal unit-dose device containing an opioid formulation as a medicament for migraine headaches. The skilled artisan would reasonably recognize the motivation of combining the teachings of Weinstein, Levin, and Ward-Smith at the time of the

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current invention due to these said references encompassing same subject matter of said current invention.

Applicants' further assert that Example 1 clearly demonstrates that the test device (the unit dose system), which produces the claimed plume geometry, provides an unexpectedly higher butorphanol concentration in the blood plasma relative to the prior art, multi-dose device. See, for example, Figure 1 and the discussion of Figure 1 appearing on page 16 of the application. In particular, page 16, lines 7-9 of the application (as amended by Preliminary Amendment A) states, "[t]he mean levels of butorphanol from analysis of the subject's blood plasma reported in pg/ml are plotted against time in Figures 1 and 2. The concentration of drug for the unit-dose system was unexpectedly higher than that of the multi-dose system (page 11, 1st full paragraph)

In response, applicant is completely silent about the *particular* plume geometry that should be produced in order to provide the unexpected results allegedly described in Example 1 of instant specification commensurate in scope of claimed invention.

The Example 1 of instant specification is not clear or concise in regard to proper description and/or explanation directed to how the test device achieves 10% higher area under the curve and 10% higher serum levels as compared to the reference device (page 11).

Additionally, at page 4 of the previous Office Action, there was a rejection over instant claims 63- 64 regarding the meaning of "Dv". However, Applicants have not adequately clarified the meaning of said term in the Remarks. In consideration of the absence of a specifically required response, the rejection remains proper and is maintained.

Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 53 - ~~67~~ and ~~70-72~~ are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which applicant regards as the invention.

Instant claim 53 discloses no sufficient explanation or definition of the alleged value "Dv". The specification vaguely suggests on page 10 of revised version that there is a direct relation of this value to "mean span" or "droplet size distribution." Additionally, in the applicants' originally filed specification, the term distribution volume is disclosed in reference on page 27, however, there is no suggestion in the instant Specification of this having any relation to the alleged value "Dv".

Claim Rejections- 35 U.S.C. 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole

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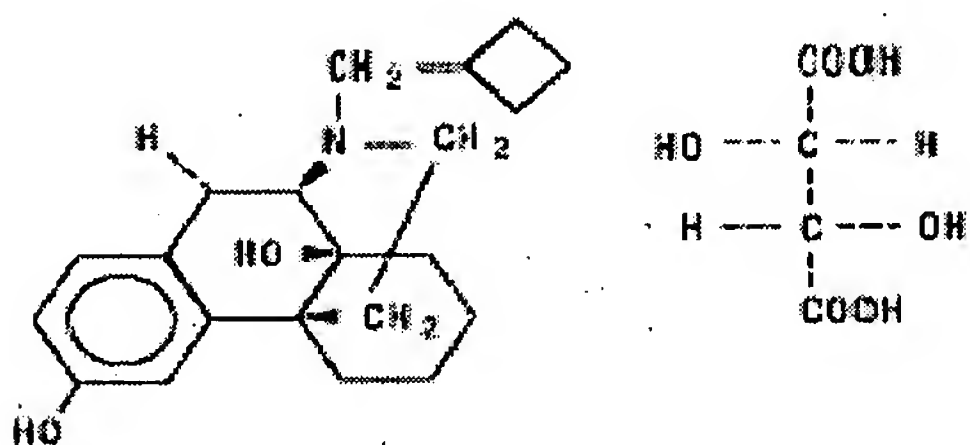
would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 53-59 and 62-67, 70, and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weinstein et al. (USPN 5437267) and Levin, B. (PGPUB US 2001/0004644 A1) in view of Ward-Smith, S., (Semi-automated testing of nasal sprays. (Nasal Spray Testing, Pharmaceutical Technology Europe, (2002), pages 1-9).

For evidentiary purposes, applicant discloses butorphanol tartrate in instant claims 54 and 71 which has an intranasal delivery formulation device system called Stadol NS®, Bristol-Myers Squibb in 1991 was approved by the FDA for marketing as a prescription medication (A Brief History of Bristol-Myers Squibb, 2007, Newsroom, page 3, 8th paragraph).

Additionally for evidentiary purposes:

Butorphanol tartrate is a synthetically derived opioid agonist-antagonist analgesic of the phenanthrene series. The chemical name is (-)-17-(cyclobutylmethyl) morphinan- 3, 14- diol [S-(R*, R*)] - 2,3 - dihydroxybutanedioate (1: 1) (salt). The molecular formula is C₂₁H₂₉NO₂, C₄H₆O₆, which corresponds to a molecular weight of 477.55 and the following structural formula:



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Butorphanol tartrate is a white crystalline substance. The dose is expressed as the tartrate salt. One milligram of the salt is equivalent to 0.68 mg of the free base. The n-octanol/aqueous buffer partition coefficient of butorphanol is 180:1 at pH 7.5.

STADOL NS (butorphanol tartrate) is an aqueous solution of butorphanol tartrate for administration as a metered spray to the nasal mucosa. Each bottle of STADOL NS contains 2.5 mL of a 10-mg/mL solution of butorphanol tartrate with sodium chloride, citric acid, and benzethonium chloride in purified water with sodium hydroxide and/or hydrochloric acid added to adjust the pH to 5.0. The pump reservoir must be fully primed (see PATIENT INSTRUCTIONS in HOW SUPPLIED) prior to initial use. After initial priming each metered spray delivers an average of 1.0 mg of butorphanol tartrate and the 2.5 mL bottle will deliver an average of 14–15 doses of STADOL NS. If not used for 48 hours or longer, the unit must be reprimed (see PATIENT INSTRUCTIONS in HOW SUPPLIED). With intermittent use requiring repriming before each dose, the 2.5 mL bottle will deliver an average of 8–10 doses of STADOL NS depending on how much repriming is necessary. (RXLIST monographs; The Internet Drug Index, (2007), Butorphanol Tartrate; Description, pages 1 and 2). Above reference discloses general specifications which is obvious over the subject matter in applicant's invention in that an opioid intranasal delivery device is taught with ingredients that are not identical but contain similar constituents as disclosed in instant claims.

Weinstein et al. teach a device for the intranasal delivery of a medicament regimen to the nasal membranes for the treatment of such conditions as rhinitis (Abstract). Referenced Figure 1A depicts a perspective view of another embodiment of invention including 2 (in comparison to 1 or more claimed in instant claim 53) medicament canisters/chambers. The term chamber is

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interchangeable with the term vessel of instant claim 53. All other depictions for Figures 2 through Figure 7 incorporate the use of more than two medicament canisters with variations in configuration thereof for optimal therapeutic delivery (Drawing sheets 1-3, columns 3-8).

Weinstein et al. does not teach use of an opioid formulation in referenced device. Additionally, Weinstein et al. does not teach a description of spray plume actuation or volume median measurements in terms of Dv parameters.

Levin teaches the practicing methods comprising intranasally administering to the patient a pharmaceutical composition comprising a local anesthetic. Levin further discloses butorphanol tartrate for use in intranasal device for muscular headaches (page 2, section [0018]; page 21, section [0200]; page 39, claim 24).

However, Levin, too, does not teach a description of spray plume actuation or volume median measurements in terms of Dv parameters.

However, Ward-Smith, which teaches nasal spray formulations consist[ing] of the drug suspended or dissolved in an aqueous medium, which is filled into a bottle with a metered spray pump. Pump actuation by the patient delivers the drug in fine droplets into the nasal cavity. The pump is an integral part of the whole assembly and plays a crucial role in delivering an accurate dose to the correct absorption site. Of particular importance is the droplet size distribution produced by the pump, which must be optimized to increase nasal deposition and minimize lung deposition or absorption in the gastrointestinal tract (page 1, 1st paragraph). Further, Ward-Smith encompasses the spray droplet size ranges disclosed by instant claims with a description of the Spraytec with Nasal spray Actuator with a 200mm Fourier lens, [which] is [...] most typically used in this application, allowing measurements in the 1-400 [micro]m size range.

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Further, Ward-Smith teaches the measurements at three different distances between the laser diffraction measurement zone and the tip of the pump (measurements of 3,6, and 9 cm) (page 3, Experimental, 4th sentence). Independent claim 53 and dependent claims 62-70 discloses a positioning of the device 1 cm and 5 cm away, respectively from a laser detection pathway. Ward-Smith teaches nasal spray formulations consist[ing] of a drug suspended or dissolved in an aqueous medium same as disclosed in instant claim 58. Laser diffraction as a technique for particle sizing is taught (page 2 and 3, Droplet sizing using laser diffraction). Multiple measurements are required for each measurement point to assess the measurement precision. The 10th, 50th and 90th percentiles (Dv10, Dv50 and Dv90) must be reported for the size distributions measured during each stage. The span of the size distribution must also be reported ($\text{Span} = [\text{Dv90} - \text{Dv10}/\text{Dv50}]$) according to Ward-Smith et al. (pg 3, Experimental, 5th sentence). Instant claims 63 and 64 are obvious in view of Ward-Smith. Referenced page 6-8 teaches actual result data obtained for manual actuation pumps and as a function of pressure (semi-automated) pumps. The reference discloses ranges higher in comparison to instant claimed ranges with the exception of some examples of conclusive data. One of ordinary skill in the pertinent art would at once recognize the necessity to properly adjust the ranges.

It, therefore, would be prima facie obvious to modify the device and medicament administered in Weinstein et al. to an opioid. Accordingly, it would be obvious to modify the device of Levin, which does teach a practicing administration of butorphanol tartrate in an intranasal device. The motivation to combine would be obvious based in view of Ward-Smith, which does teach the specific parameters of efficacious administration, i.e., description of spray plume actuation, the detection of droplet size distribution, specific droplet size, etc.

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Claims 60, 61 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum et al. (Intranasal Delivery of Morphine, The Journal of Pharmacology and Experimental Therapeutics, 2001, vol.301, no.1, pages 391-400), Pezron et al. (Prodrug strategies in nasal drug delivery, Expert Opin. Ther. Patents (2002) 12(3): 331-340), and Manjushree et al. (Intranasal fentanyl provides adequate postoperative analgesia in pediatric patients, CAN J ANESTH 2001,49:2, pages 190-193) in view of Midha et al. (USPN 6127385)

Illum et al. teach the intranasal delivery of morphine, a potent narcotic analgesic, [which] produces a variety of pharmacological responses by interacting with the opioid receptors in the nervous system (page 391, 1st paragraph). Further, Illum et al. teach butorphanol as a practicing analgesic agent that can be effectively and rapidly absorbed from the nasal cavity (page 391, 3rd paragraph). Additionally, Illum et al. teach a pH range of 4.02 and 3.81, respectively which are specific to the broad pH range (pH of about 3 to about 6) disclosed in instant independent claim 53 (page 392, Formulation Preparation, 2nd and 3rd paragraph).

Illum et al. does not teach the intranasal opioid formulation with citrate buffered water or a sweetener. Illum et al. teach said formulation with an absorption-promoting agent such as chitosan.

Pezron et al. teach strategies for enhanced nasal drug delivery via taste modification of these bitter moieties by use with moieties that lack bitterness (page 337, Miscellaneous applications, 2nd paragraph).

Pezron et al. does not teach nasal drug formulation with a sweetener to mask the bitter taste due to administration.

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Manjushree et al. teach the well-established use of the intranasal opioid fentanyl with the nasal carrier citrate in the formulation (page 191). Further, Manjushree et al. teach the scope of prolonged use of fentanyl citrate without any adverse effects.

Manjushree et al. does not teach an intranasal opioid with a sweetener or flavoring agent.

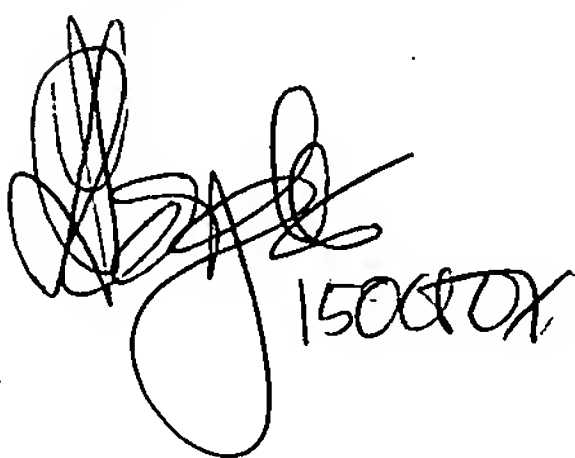
However, the Examiner refers to Midha et al., which teach an embodiment of a nasal formulation containing [active agent] dissolved in aqueous or non-aqueous solvent, an antioxidant and aromatic oils as flavoring agents (column 4, lines 59 to 63). In instant claim 61, aromatic oils are disclosed as rosemary oil, spearmint oil, thyme oil, etc. Instant claim 72 specifically discloses sucrose, but Midha et al. does not teach sucrose. However, it would have been obvious to interchange flavoring agents based on the list disclosed within instant claim 61.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TEB


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SUPERVISORY PATENT EXAMINER